ACIP Meeting

February 24, 2010

Fluzone® High-Dose Vaccine

High-dose Influenza Virus Vaccine for Persons 65 Years of Age and Older

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Influenza Among Persons 65 Years of Age and Older

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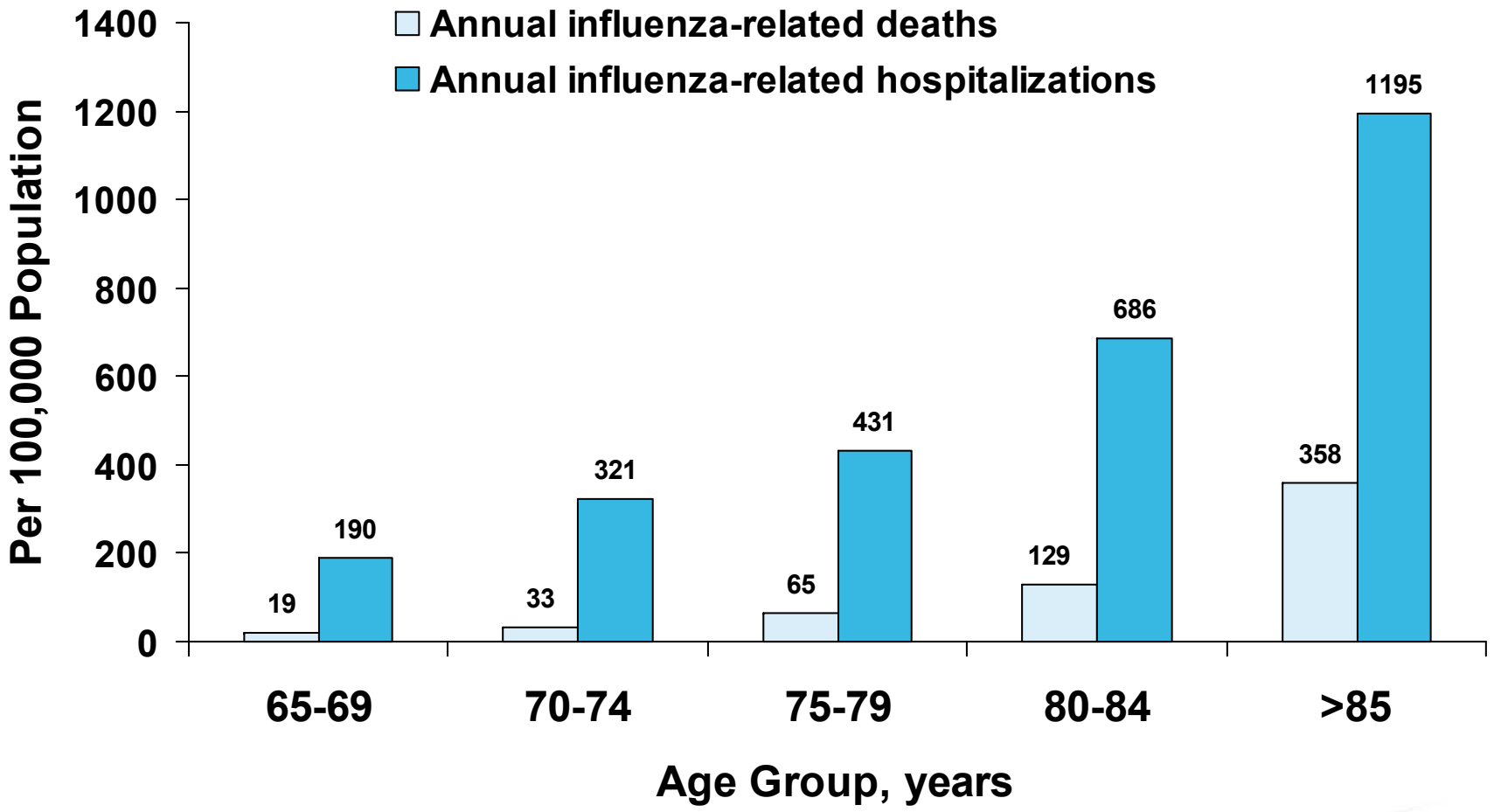
CDC: Influenza-associated hospitalization and death rates, by age group, 1976–2000



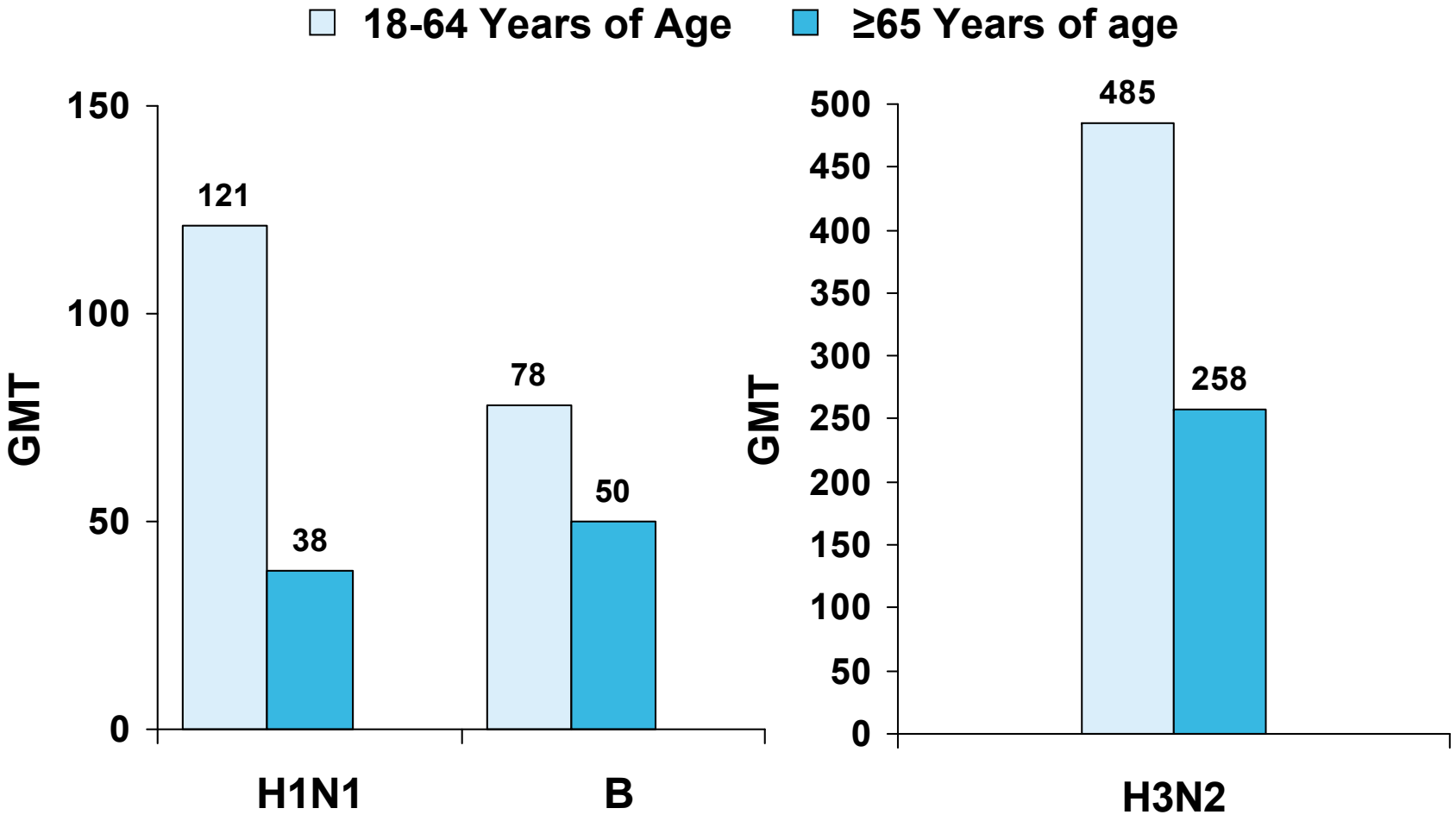
Thompson WW, et al. *J Infect Dis*. 2006;194(suppl 2):S82-S91.

Older Adults Are More Prone to Influenza-Related Complications

- Adults ≥65 years of age comprise 15% of the US population, but account for 65% of hospitalizations and 90% of deaths attributable to influenza and its complications
- Among older adults, influenza causes an estimated 3.2M illnesses, 136K hospitalizations, and 36K deaths per year with annual direct medical costs of $4.2B and total economic burden of $56.1B
- Influenza vaccines provide substantial protection, but older adults respond less well to standard-dose influenza vaccines compared with younger adults
  - Lower antibody titers leave older adults more vulnerable to serious infection and severe complications

Thompson WW, et al. *J Infect Dis*. 2006;194(Suppl. 2):S82-S91. Zheng B, et al. *J Immunol*. 2007;179(9):6153-6159. Molinari NM, et al. *Vaccine* 2007;25(27):5086-96.

Postvaccination GMTs, Standard-Dose Fluzone Vaccine, Younger vs Older Adults



Sanofi Pasteur annual release study GRC41

Decreased Immunity Against Influenza Is a Result of Aging and Immunosenescence

- Declining humoral and cellular immunity, a result of aging, increases susceptibility of older adults to infection
- Older adults have decreased immunologic responses to vaccines due to immunosenescence
- Age-related changes in T-cell subsets and in cytokine production profiles affects the magnitude, quality, and persistence of antibody responses to vaccines

In response to increasing calls for vaccines to improve antibody responses and prevent influenza among older adults, sanofi pasteur developed Fluzone High-Dose vaccine

Zheng B, et al. *J Immunol*. 2007;179(9):6153-6159. Doria G, et al. *Mech Ageing Dev*. 1997;96(1-3):1-13.
Siegrist CA. The immunology of vaccination. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Saunders; 2008.

Fluzone High-Dose Vaccine Study FIM05 (Phase III)

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Lot Consistency, Safety, Immunogenicity of Fluzone High-Dose, Study FIM05 (Phase III)

Study Design

- Phase III, multicenter, randomized double-blind study
  - 3876 participants 65 years of age or older
  - Randomized 2:1 to receive either High-Dose (HD; 60µg HA per strain) or Standard-Dose (SD; 15µg HA per strain)
    - Participants in the High-Dose group were further randomized to receive 1 of 3 different lots of the vaccine
  - Blood specimens obtained pre-vaccine and Day 28 for evaluation of influenza antibodies
  - Safety data collected by diary card (1 week), visits (4 weeks), and telephone calls (up to 6 months) postvaccination

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Lot Consistency, Safety, Immunogenicity of Fluzone High-Dose, Study FIM05 (Phase III)

Primary and Secondary Endpoints

- **Primary Endpoints**
  - Immunogenicity – Lot Consistency
  - Immunogenicity – Superiority
    - GMTs
    - 4-fold rise rates
- **Secondary Endpoints**
  - Immunogenicity – Seroprotection rates
  - Solicited safety and reactogenicity
  - Unsolicited AEs and SAEs

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Solicited Injection Site Reactions, Study FIM05 (Phase III)

Intensity of Injection-site Reactions Day 0 to Day 7 Postvaccination

		High-Dose (N = 2573)		Standard-dose (N = 1260)	
	Intensity	%	95% CI	%	95% CI
Pain	Any	35.6	(33.7; 37.5)	24.3	(21.9; 26.8)
	Grade III	0.3	(0.2; 0.7)	0.2	(0.0; 0.6)
Erythema	Any	14.9	(13.6; 16.4)	10.8	(9.1; 12.6)
	Grade III	1.8	(1.3; 2.4)	0.6	(0.2; 1.1)
Swelling	Any	8.9	(7.9; 10.1)	5.8	(4.6; 7.2)
	Grade III	1.5	(1.1; 2.1)	0.6	(0.3; 1.2)

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Solicited Systemic Reactions, Study FIM05 (Phase III)

Intensity of Systemic Reactions Day 0 to Day 7 Postvaccination

	High-Dose (N=2573)		Standard-dose (N=1260)	
Reaction	**%**	95% CI	**%**	95% CI
Any Myalgia	**21.4**	(19.8; 23.0)	**18.3**	(16.2; 20.5)
Grade III	**1.6**	(1.2; 2.2)	**0.2**	(0.0; 0.7)
Any Malaise	**18.0**	(16.5; 19.5)	**14.0**	(12.1; 16.0)
Grade III	**1.6**	(1.1; 2.2)	**0.6**	(0.2; 1.1)
Any Headache	**16.8**	(15.3; 18.3)	**14.4**	(12.5; 16.5)
Grade III	**1.1**	(0.7; 1.6)	**0.3**	(0.1; 0.8)
Any Fever	**3.6**	(2.9; 4.4)	**2.3**	(1.5; 3.3)
Grade III	**0.0**	(0.0; 0.2)	**0.1**	(0.0; 0.4)

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Immediate and Unsolicited AEs, and SAEs, Study FIM05 (Phase III)

- Adverse events occurring in the 30 minutes following vaccination were comparable; 0.3% in both groups
- Rates of unsolicited adverse events within 28 days postvaccination were comparable; 22% in both groups
- Rates of SAEs were comparable; 6.1% High-Dose vaccine, 7.4% Standard-Dose vaccine
  - Only 2 SAEs were reported by investigators as vaccine related: an exacerbation of Crohn's disease 2 days after vaccination with High-Dose vaccine, and a new diagnosis of myasthenia gravis 1 month after vaccination with Standard-Dose vaccine
- No deaths occurred between Day 0 and Day 28
  - 23 deaths were reported after Day 28 (0.6% in both groups)
  - All deaths were deemed unrelated to vaccination

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

FIM05: Superiority Criteria for Immunogenicity

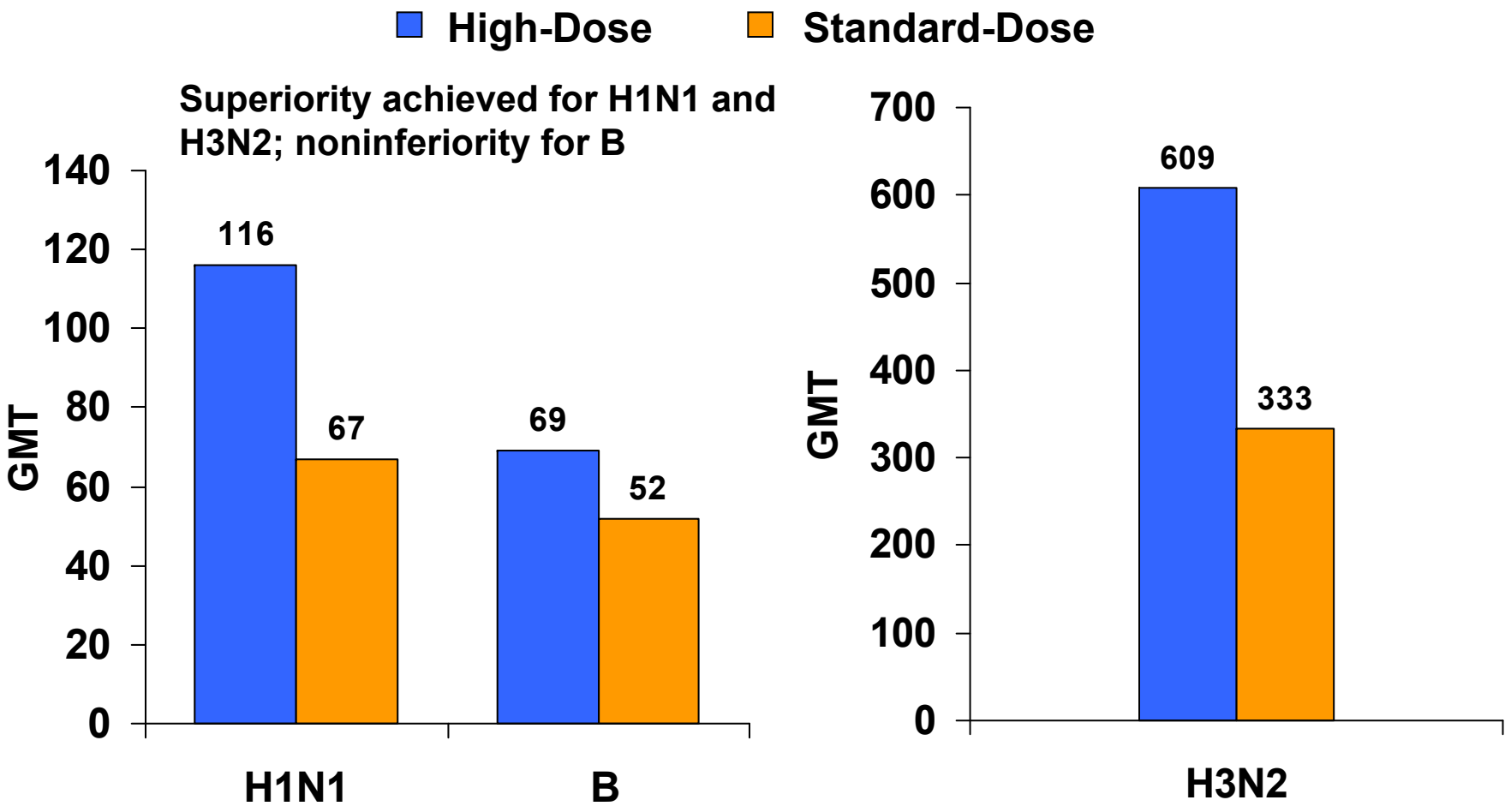
Rigorous approach applied to the superiority assessments

- ***For Fluzone High-Dose vaccine to be considered superior to Fluzone Standard-Dose vaccine, demonstration of superiority for at least two of the three vaccine strains without inferiority for any strain was required***

	Lower Bound of 2-sided 95% Confidence Interval (CI)	
Superiority Endpoints	**Traditional**	**FIM05 Study**
Ratio of GMTs (HD / SD)	**>1.0**	**>1.5**
Difference in 4-fold rise rates (HD – SD)	**>0%**	**>10%**

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Geometric Mean Titers Postvaccination, Study FIM05 (Phase III)

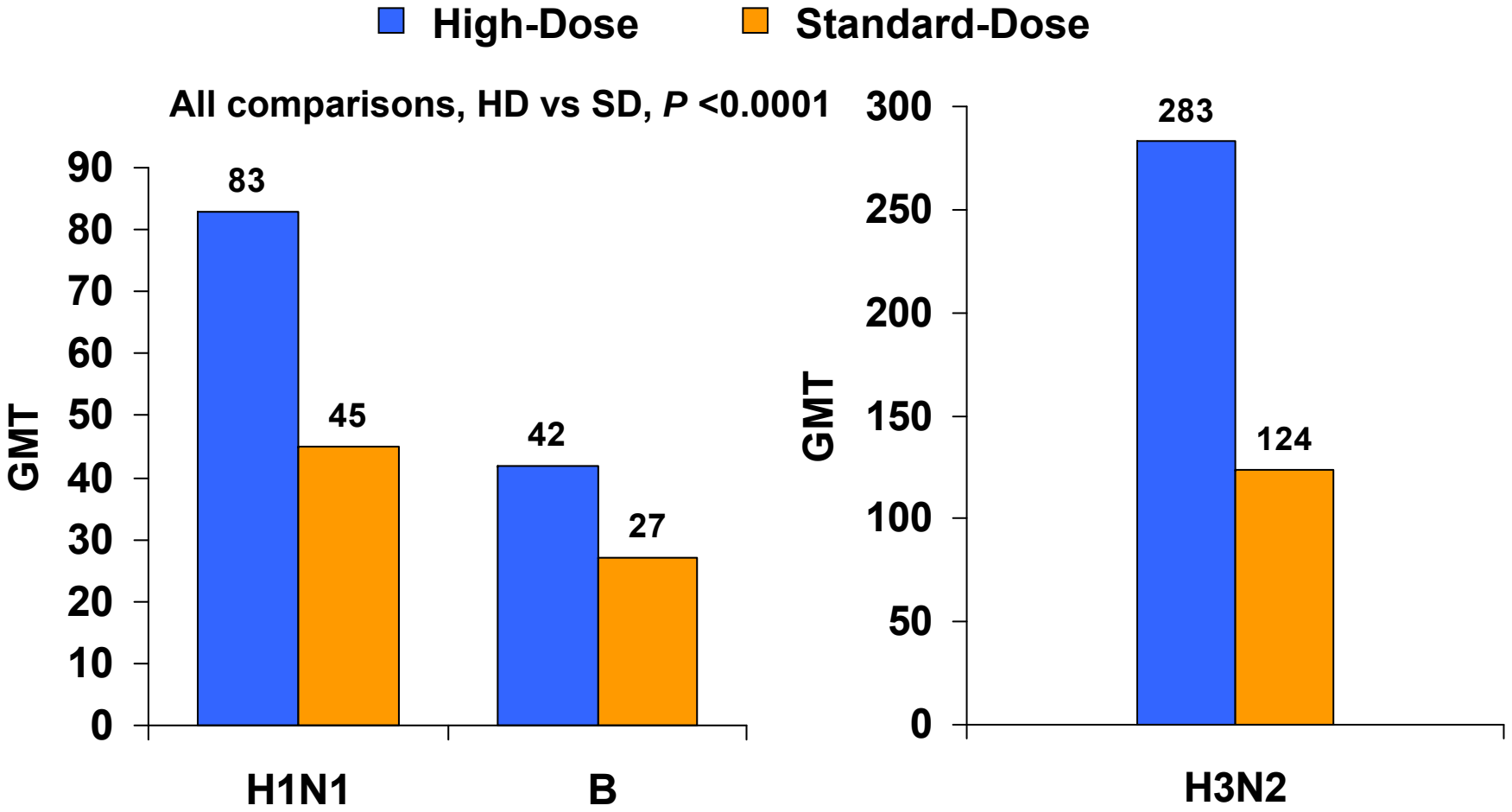


All comparisons, HD vs SD, *P* <0.0001

HD: N = 2576; SD: N = 1275

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

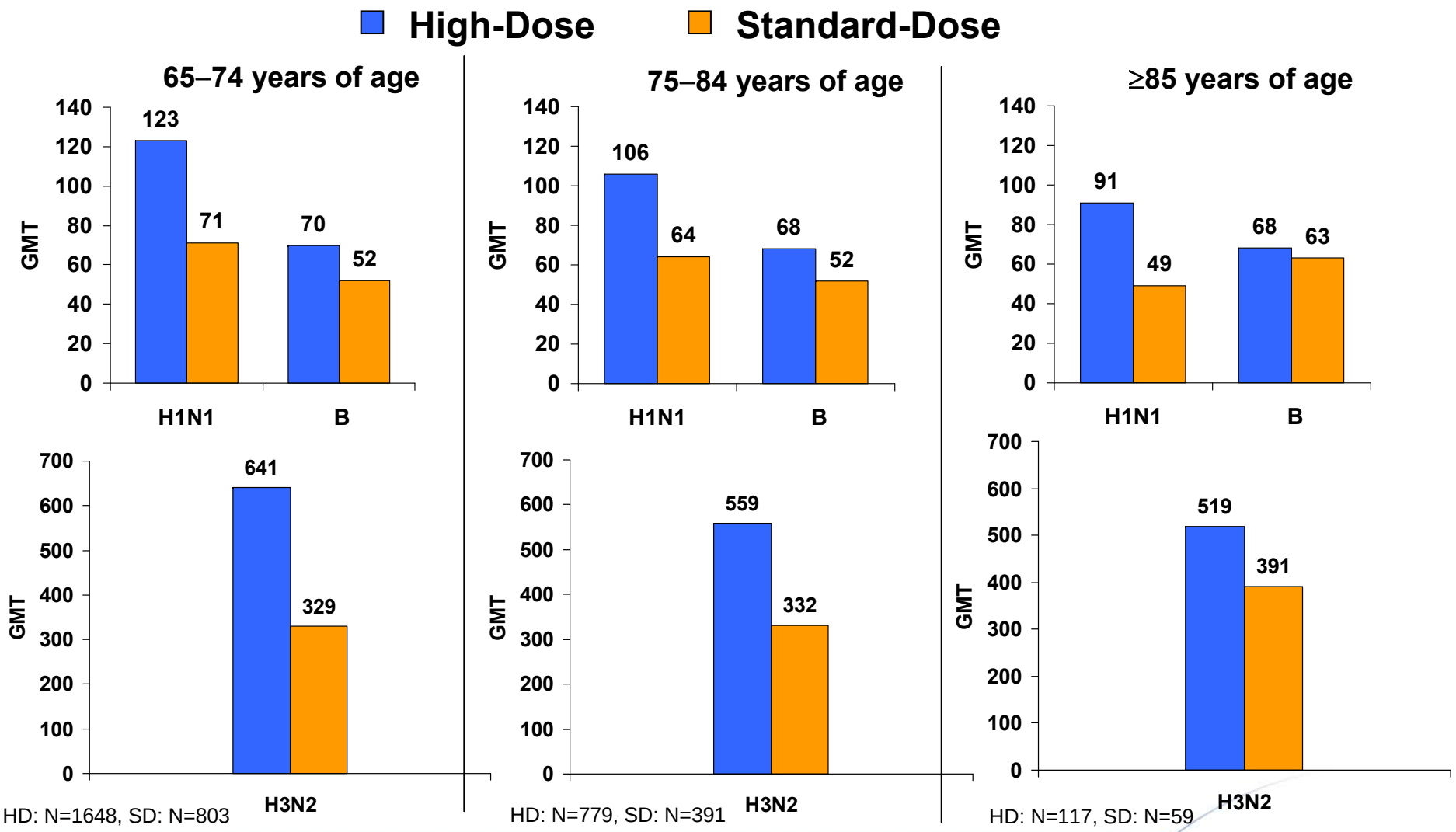
Postvaccination GMTs for Participants with Negative Baseline Titers (<1:10), Study FIM05



HD: N = 265 (H1N1); 193 (H3N2); 519 (B); SD: N = 121 (H1N1); 102 (H3N2); 278 (B)

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

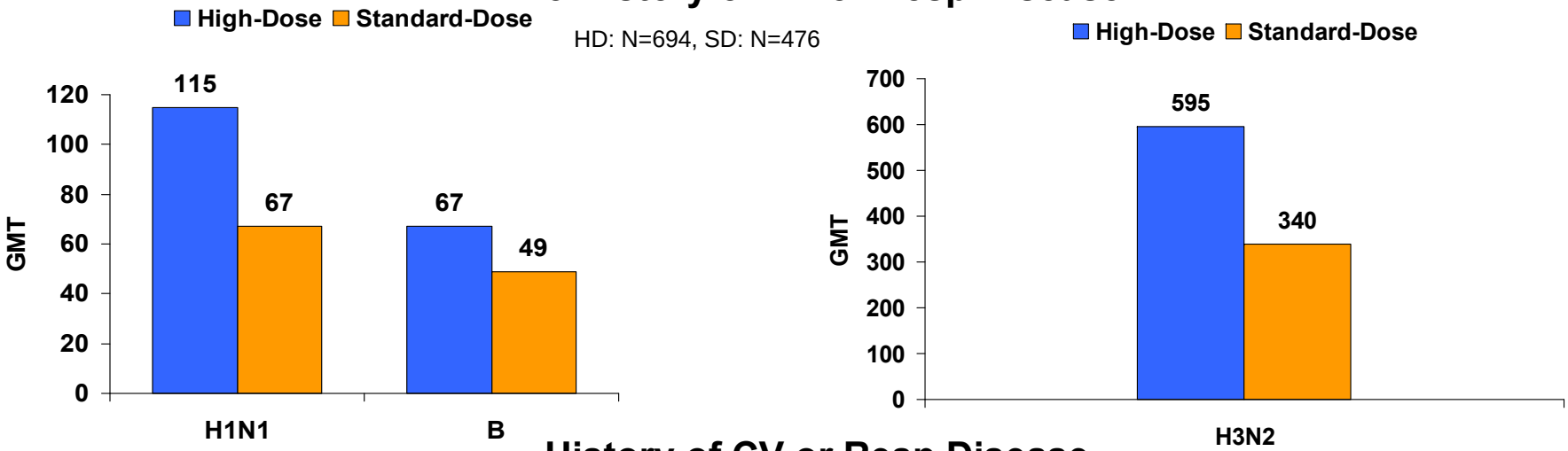
Geometric Mean Titer by Age, Study FIM05 (Phase III)



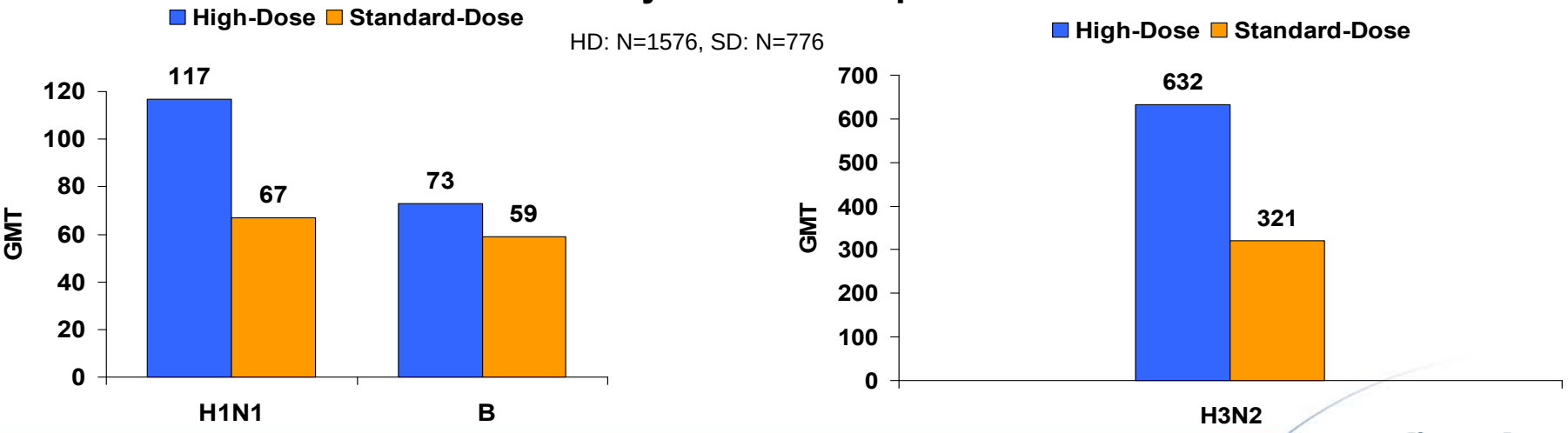
Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Geometric Mean Titer by Health Risk, Study FIM05 (Phase III)

No History of CV or Resp Disease



History of CV or Resp Disease



Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Superiority Endpoints, Study FIM05 (Phase III)

Based on FDA criteria, the immunogenicity of Fluzone High-Dose vaccine was superior to Fluzone Standard-Dose vaccine

Strain	GMT Ratios HD / SD (95% CI)	4-Fold Rise Rates HD – SD (95% CI)	Met Pre-Defined Endpoints
H1N1	1.7 (1.6-1.8)	25% (22-28%)	Superiority
H3N2	1.8 (1.7-2.0)	18% (15-22%)	Superiority
B	1.3 (1.2-1.4)	12% (9-15%)	Noninferiority

Differences maintained for persons <75 yrs and ≥75 yrs of age, persons with or without a history of cardiovascular or respiratory disease, and both males and females

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Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Summary and Conclusions, Study FIM05 (Phase III)

- Rates of solicited injection-site and systemic reactions were more frequent with High-Dose vaccine, but were transient and well-tolerated
- Fluzone High-Dose vaccine was significantly more immunogenic than Standard-Dose vaccine against all 3 strains
  - GMTs, 4-fold rise rates, and seroprotection rates
  - Benefit maintained across age, underlying condition, and gender
  - Met pre-specified FDA-defined superiority criteria
- Fluzone High-Dose vaccine induced superior antibody responses compared with Standard-Dose vaccine against H1N1 and H3N2 strains (70% and 80% higher); noninferior against B strain (30% higher)

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.

Fluzone High-Dose Licensure and Next Steps

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Fluzone High-Dose Vaccine Licensure and Availability

- CBER licensed Fluzone High-Dose vaccine on December 23, 2009
- Fluzone High-Dose vaccine will be available for the upcoming 2010-2011 immunization season
- Post-licensure efficacy trial began in September, 2009

Post-Licensure Efficacy Trial, Study FIM07, Study Design

- 26-33K subjects ≥65 years of age
- 3-year study
- Randomized, blinded, 2:1 ratio of HD and SD vaccines
- Postvaccination blood draw from one-third of subjects
- Active surveillance for ILI
- Laboratory confirmation by culture and PCR
- SAEs monitored for 180 days postvaccination
- Superiority criterion: lower bound of the 95% CI for relative vaccine efficacy of Fluzone High-Dose compared with Standard-Dose greater than 9.1%

Post-Licensure Efficacy Trial, Study FIM07, Status

- First subject enrolled September 22, 2009
- Enrollment for Year 1 completed on November 7th with 9178 subjects from 99 sites throughout the US
- Blood specimens collected post-vaccination from one-third of the participants
- Surveillance for ILI and collection of respiratory specimens for culture and PCR is ongoing
- Independent Data Monitoring Committee will review safety and efficacy data during the trial

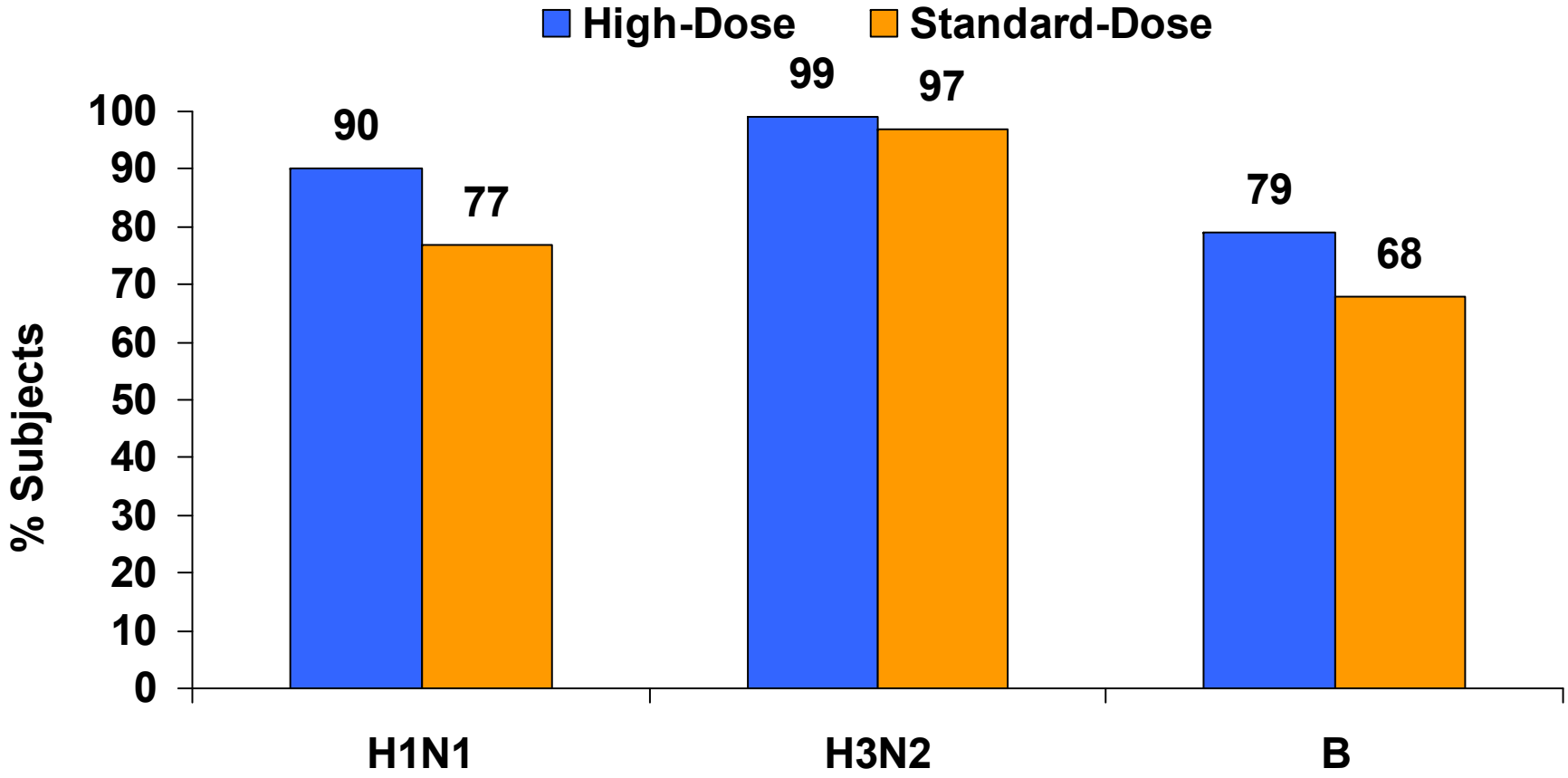
Status of Fluzone High-Dose Vaccine

- Fluzone High-Dose vaccine will be available for the upcoming 2010-2011 immunization season
- Preservative-free, non-adjuvanted, 0.5mL pre-filled syringes
- Began accepting reservations on February 15, 2010
- Medicare Part B coverage expected

Thank You

Back-up Slides

Seroprotection Rates, Study FIM05 (Phase III)



Seroprotection rate is the percentage of vaccine recipients with a serum HAI titer of at least 1:40 after vaccination

All comparisons, HD vs SD, *P* <0.0001

Sanofi Pasteur, Study FIM05. Falsey AR, et al. *J Infect Dis* 2009;200:172-180.